J Med Genet 1998;35:482–490

Maternal age specific risk rate estimates for Down syndrome among live births in whites and other races from Ohio and Metropolitan Atlanta, 1970-1989

Carl A Huether, Jennifer Ivanovich, Betsy S Goodwin, Eric L Krivchenia, Vicki S Hertzberg, Larry D Edmonds, Daniel S May, Jean H Priest

Department of Biological Sciences, University of Cincinnati, Cincinnati, OH 45221-0006, USA
C A Huether
J Ivanovich*
B S Goodwin†
E L Krivchenia‡

Department of Environmental Health, University of Cincinnati, Cincinnati, OH, USA
V S Hertzberg§

Division of Birth Defects and Developmental Disabilities, National Center for Environmental Health, Centers for Disease Control and Prevention, Atlanta, GA, USA
L D Edmonds

National Center for Chronic Diseases Public Health Prevention, Centers for Disease Control and Prevention, Atlanta, GA, USA
D S May

Department of Medical Genetics, Emory University, Atlanta, GA, USA
J H Priest¶

Correspondence to:
Dr Huether.
*Present address: Division of Medical Genetics, Washington University School of Medicine, St Louis, MO, USA.
†Present address: Department of Obstetrics/Gynecology, Ohio State University, Columbus, OH, USA.
‡Present address: Division of Reproductive Genetics, Department of Obstetrics/Gynecology, Hutzel Hospital, Detroit, MI, USA.
§Present address: Department of Epidemiology and Biostatistics, Emory University, Atlanta, GA, USA.
¶Present address: Department of Medical Genetics, Shodair Hospital, Helena, MT, USA.

Received 18 September 1997
Revised version accepted for publication
8 December 1997

Abstract

Our primary objective was to estimate, by one year and five year intervals, maternal age specific risk rates for Down syndrome among whites and among other races from two different populations, metropolitan Atlanta and south west Ohio, using live birth and prenatally diagnosed cases ascertained during 1970-1989. The five year estimates were also calculated separately for each of the five four year periods during these 20 years. Additionally, we compared two different methods of estimating these risk rates by using a third population of whites, and compared two different statistical methods of smoothing the risk rates.

The results indicate good agreement between the metropolitan Atlanta and south west Ohio estimates within races, but show a statistically significant difference between the two race categories. Because 86% of live births in the "other races" category in the combined population are to blacks, these data may be seen as the first estimates of maternal age specific risk rates for Down syndrome among blacks calculated by one year intervals.

We found excellent agreement in the risk rate estimates among the five four year time periods, between the estimates obtained by using the two different methods of estimation, and between the estimates obtained using the two different methods of statistical smoothing.

Our estimated risk rates for white women in their 20s strongly reinforce those from previous studies currently being used for genetic counselling purposes. While we did find somewhat higher rates for women under 20, and increasingly higher rates for those over 30 years of age, these differences are not substantial. Thus, this study in general supports the risk rates estimated from data collected mostly during the 1960s and 1970s.
(*J Med Genet* 1998;35:482–490)

Keywords: Down syndrome; risk rate estimates

Since Down syndrome was confirmed as an autosomal trisomy in 1959, seven studies have estimated single year maternal age specific risk rates for Down syndrome in liveborn populations outside the United States.[1–7] Another three such studies have been published from data sets within the United States.[8–10] Fifteen or so additional studies world wide have estimated maternal age risk rates by five year age intervals.[11] Most of the single year studies are based upon births occurring during the 1960s and early 1970s, and only one includes data after 1980, based upon data from South Australia.[7] All estimates of single year maternal age specific rates currently available use data from white populations only. When these single year rates have been compared, they generally have been found to be in agreement. However, investigators conducting a study in Rhode Island found higher age specific rates, calculated by five year age intervals, than those found in either Atlanta or New York.[12]

The objectives of this study were: (1) to estimate maternal age specific risk rates for Down syndrome (in both one year and five year intervals) among whites and among other races in metropolitan Atlanta and in south west Ohio during 1970-1989; (2) to compare these estimated rates between the two race categories and among three different populations; (3) to determine whether risk rates changed during the 20 year period; (4) to compare two different methods of estimating these risk rates among whites, as well as to compare two different statistical methods of smoothing these estimates; and (5) to provide current single year maternal age specific risk rate estimates for two race categories from the combined populations for use in genetic counselling.

There are several reasons for providing estimates of maternal age specific risk rates for Down syndrome from current data: increased use of prenatal diagnosis and chemical screening methods has increased the importance of these estimates; the completeness and accuracy of data sets have improved with our greater awareness of Down syndrome and the use of karyotype analysis for definitive diagnosis; because of uncertainty about the confounding effects of demographic changes, improved ascertainment, and increased prenatal diagnosis, there have been conflicting reports on whether maternal age specific risk rates are changing over time; and estimates for races other than whites are both needed and now possible through the availability of better data sets.

The principal data sets used to estimate rates for both whites and other races were from south west Ohio and metropolitan Atlanta for 1970-1989; populations of both areas are

Table 1 Number of live births and fetuses with Down syndrome and total live births for whites in south west Ohio and metropolitan Atlanta, and combined regression derived risk rates, by single year maternal age, 1970–1989

Mat age	DS live births	DS fetuses	Total DS cases*	Ohio live births	Rate†	DS live births	DS fetuses	Total DS cases*	Atlanta live births	Rate†	Regression derived Rate‡	Regression derived Ratio‡
≤15	4	0	4	4347	0.92	1	0	1	2421	0.41	0.82	1:1220
16	5	0	5	9117	0.55	6	0	6	4591	1.31	0.75	1:1333
17	9	0	9	16 193	0.56	6	0	6	7882	0.76	0.71	1:1408
18	12	0	12	22 743	0.53	5	0	5	11 290	0.44	0.67	1:1492
19	22	0	22	29 146	0.75	12	0	12	14 183	0.85	0.65	1:1538
20	24	0	24	31 901	0.75	5	0	5	16 202	0.31	0.64	1:1562
21	21	0	21	33 967	0.62	13	0	13	17 898	0.73	0.63	1:1587
22	22	0	22	36 608	0.60	11	1	11.7	19 748	0.59	0.64	1:1562
23	34	0	34	38 835	0.88	7	0	7	21 358	0.33	0.66	1:1515
24	30	0	30	39 365	0.76	25	0	25	22 653	1.10	0.68	1:1470
25	21	0	21	39 287	0.53	18	0	18	23 695	0.76	0.72	1:1389
26	38	2	39.5	38 354	1.03	15	0	15	24 607	0.61	0.78	1:1282
27	33	0	33	36 830	0.90	17	0	17	24 518	0.69	0.85	1:1176
28	35	0	35	33 335	1.05	22	1	22.7	23 525	0.96	0.94	1:1064
29	34	0	34	29 679	1.15	20	0	20	22 481	0.89	1.06	1:943
30	27	0	27	25 129	1.07	29	0	29	19 701	1.47	1.21	1:826
31	26	0	26	20 883	1.25	18	2	19.5	16 778	1.16	1.40	1:714
32	24	1	24.7	16 639	1.48	19	2	20.5	13 884	1.48	1.65	1:606
33	26	0	26	13 361	1.95	20	1	20.7	11 396	1.82	1.97	1:508
34	24	3	26.2	10 592	2.47	14	2	15.5	9115	1.70	2.39	1:418
35	22	5	25.7	7936	3.24	10	10	17.4	7240	2.40	2.94	1:340
36	19	6	23.5	6048	3.89	10	10	17.4	4845	3.59	3.68	1:272
37	25	9	31.7	4462	7.10	6	10	13.4	3702	3.62	4.68	1:214
38	18	2	19.5	3209	6.08	5	9	11.7	2665	4.39	6.03	1:166
39	17	4	20	2494	8.02	5.6	9	12.3	1687	7.29	7.88	1:127
40	21	5	24.7	1755	14.07	10	12	18.9	1030	18.35	10.46	1:96
41	9	4	12	1107	10.84	1	6	5.4	687	7.86	14.08	1:71
42	9	4	12	760	15.79	3	5	6.7	456	14.69	19.22	1:52
43	12	2	13.5	400	33.75	1	4	4	189	21.16	26.58	1:38
44	10	1	10.7	234	45.73	4	3	6.2	123	50.41	37.18	1:27
≥45	6	1	6.7	179	37.43	4	3	6.2	85	72.94	52.55	1:19
Total	639	49	675.4	554 895	1.22	342.6	409.4	90	350 635	1.17		

*Down syndrome live births and fetuses (× 0.74 probability of survival).
†Per 1000 live births.
‡Smoothed rates per 1000 live births using regression model on combined data.

believed to be highly ascertained for both live births with Down syndrome and for fetuses diagnosed prenatally before being electively terminated. The data sets are based upon cases of Down syndrome among liveborn infants that were confirmed from multiple sources of ascertainment and are corrected for pregnancies terminated following prenatal diagnosis.

Methods

METROPOLITAN ATLANTA DATA SET

Data on all live births with Down syndrome born to residents in the five county region of metropolitan Atlanta during 1970-1989 were obtained from the Metropolitan Atlanta Congenital Defects Program (MACDP). This surveillance system is conducted by the Centers for Disease Control and Prevention (CDC), whose staff actively abstract numerous sources of information to achieve what is believed to be essentially complete ascertainment of cases.[13] Data on fetuses with Down syndrome detected through prenatal diagnosis were obtained through extensive review of records from the six cytogenetic laboratories known to be analysing amniotic fluid from pregnant women who were residents of the metropolitan area. (No choronic villus sampling procedures were carried out during the time period.) These individual laboratories are indicated in the acknowledgment section. Other national laboratories doing karyotype analysis in the late 1980s were contacted, but none reported additional cases (a situation that is likely to be very different today). Data on live births to residents of the five county region for the 20 year period were obtained from the Georgia Department of Human Resources, Southwest Ohio Data Set.

Data on live births with Down syndrome for the same 1970-1989 time period to residents in the 10 county region of south west Ohio were obtained from multiple sources. The sources actively abstracted included records from the region's cytogenetic laboratories, obstetric hospitals' medical records, and birth certificates for the region. Additionally, some cases were uniquely ascertained through the CDC's Birth Defects Monitoring Program (which had contracted with some hospitals in the region to provide birth defects data) and, for part of the time period, Ohio's Neonatal Log, which attempted to ascertain birth defects information through hospitals reporting directly to

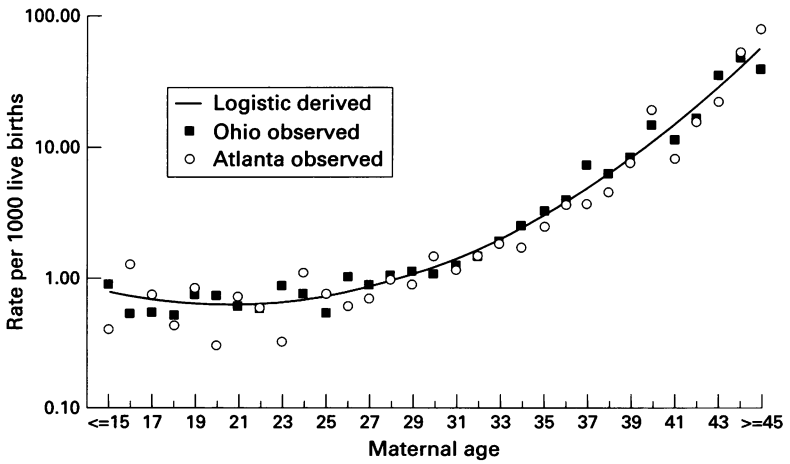

Figure 1 Single year maternal age specific observed risk rates for Down syndrome in south west Ohio and metropolitan Atlanta, and smoothed rates derived from the logistic model for whites, 1970-1989 (per 1000 live births, corrected for pregnancies terminated following prenatal diagnosis of Down syndrome).

Table 2 Number of live births and fetuses with Down syndrome and total live births for other races in south west Ohio and metropolitan Atlanta, and combined regression derived risk rates, by single year maternal age, 1970–1989

Mat age	DS	DS fetus	DS cases*	Ohio live births	DS rate†	DS	DS fetus	Atlanta live cases*	Births		Regression derived Rate†	Regression derived Ratio‡
≤15	2	0	2	4021	0.50	6	0	6	6633	0.90	0.98	1:1020
16	2	0	2	4888	0.41	5	0	5	7243	0.69	0.89	1:1124
17	4	0	4	7070	0.57	6	0	6	9559	0.63	0.81	1:1234
18	11	0	11	8672	1.27	8	0	8	11 951	0.67	0.75	1:1333
19	9	0	9	9891	0.91	10	0	10	13 464	0.74	0.71	1:1408
20	5	0	5	9768	0.51	10	0	10	13 779	0.73	0.68	1:1470
21	10	0	10	9332	1.07	12	0	12	14 014	0.86	0.66	1:1515
22	6	0	6	8707	0.69	7	0	7	13 829	0.51	0.65	1:1538
23	8	0	8	8124	0.98	8	0	8	13 214	0.61	0.65	1:1538
24	4	0	4	7371	0.54	14	0	14	12 600	1.11	0.66	1:1515
25	4	0	4	7056	0.57	12	0	12	12 076	0.99	0.69	1:1449
26	4	0	4	6331	0.63	5	0	5	11 317	0.44	0.72	1:1389
27	4	0	4	5685	0.70	10	0	10	10 567	0.95	0.77	1:1299
28	3	0	3	5217	0.58	7	1	7.7	9636	0.80	0.83	1:1205
29	5	0	5	4407	1.13	8	0	8	8745	0.91	0.91	1:1099
30	0	0	0	3996	0.00	9	0	9	7526	1.20	1.02	1:980
31	4	0	4	3253	1.23	5	0	5	6388	0.78	1.15	1:870
32	0	0	0	2786	0.00	3	0	3	5316	0.56	1.32	1:758
33	2	0	2	2071	0.97	8	0	8	4557	1.76	1.54	1:649
34	2	0	2	1663	1.20	9	0	9	3512	2.56	1.83	1:546
35	3	0	3	1493	2.01	7	1	7.7	2866	2.69	2.20	1:454
36	2	0	2	1104	1.81	6	3	8.2	2222	3.69	2.69	1:372
37	3	0	3	851	3.53	5	0	5	1634	3.06	3.34	1:299
38	2	2	3.5	757	4.62	4	1	4.7	1277	3.68	4.20	1:238
39	2	1	2.7	484	5.58	5.4	0	5.4	844	6.40	5.37	1:186
40	1	1	1.7	366	4.64	6	3	8.2	645	12.71	6.97	1:143
41	2	0	2	271	7.38	2	1	2.7	333	8.11	9.18	1:109
42	2	1	2.7	185	14.59	1	0	1	203	4.93	12.26	1:82
43	1	0	1	97	10.31	4	1	4.7	179	26.26	16.60	1:60
44	2	0	2	53	37.74	1	2	2.5	76	32.89	22.79	1:44
≥45	2	0	2	67	29.85	0	0	0	61	0.00	31.67	1:32
Total	111	5	114.6	126 037	0.91	203.4	13	212.8	206 266	1.03		

*Down syndrome live births and fetuses (× 0.74 probability of survival).
†Per 1000 live births.
‡Smoothed rates per 1000 live births using regression model on combined data.

the state. Corrections were made for false positives in the birth certificates and Neonatal Log where possible. Data on fetuses with Down syndrome were obtained from the region's four cytogenetic laboratories, which throughout this time period were essentially the sole laboratories for karyotype analysis of amniotic fluids. Contact with a number of national cytogenetic laboratories did not show any additional cases of prenatal diagnosis for women who were residents of the region. Live births to residents of the region for the 20 year period were obtained from the Division of Data Services, Ohio Department of Health.

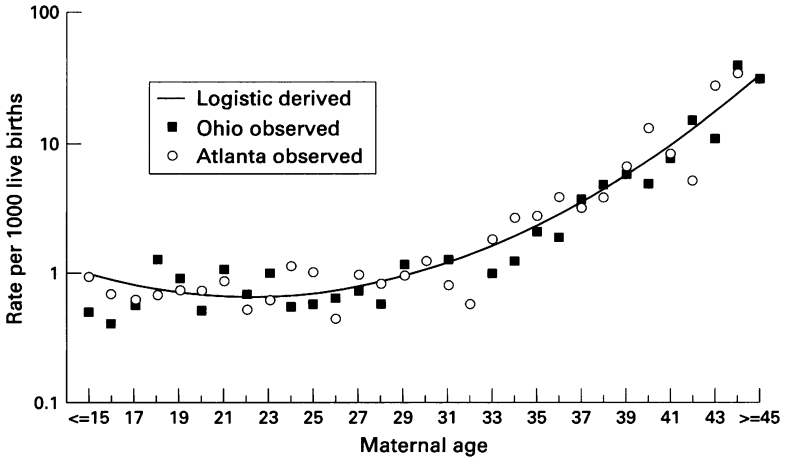

Figure 2 Single year maternal age specific observed risk rates for Down syndrome in south west Ohio and metropolitan Atlanta, and smoothed rates derived from the logistic model for other races, 1970-1989 (per 1000 live births, corrected for pregnancies terminated following prenatal diagnosis of Down syndrome).

STATE OF OHIO DATA SET

A third data set, used for estimating risk rates among whites only, is an updated revision of previously published estimates from all of Ohio for 1970-1979,[10] extended an additional four years (to 1983), and is derived from a different method of estimation. In contrast to the other two data sets, ascertainment was not complete; instead, this data set was derived from birth certificate data, corrected for both false negatives (from under-reporting) and false positives. However, like the other two data sets, these data were corrected for pregnancies terminated following prenatal diagnosis of Down syndrome. All records of live births with Down syndrome

Table 3 Regression derived rates by maternal age quinquennia based upon combined data from south west Ohio and metropolitan Atlanta in tables 1 and 2, by race, 1970–1989

Mat age	Regression derived Rate*	Range	Ratio*
Whites			
≤19	0.71	0.65–0.82	1:1408
20–24	0.64	0.64–0.68	1:1562
25–29	0.85	0.72–1.06	1:1176
30–34	1.65	1.21–2.39	1:606
35–39	4.68	2.94–7.88	1:214
40–44	19.22	10.46–37.18	1:52
≤45	52.55	—	1:19
Other races			
≤19	0.81	0.71–0.98	1:1234
20–24	0.65	0.64–0.68	1:1538
25–29	0.77	0.69–0.91	1:1299
30–34	1.32	1.02–1.83	1:758
35–39	3.34	2.20–5.37	1:299
40–44	12.26	6.97–22.79	1:44
≤45	31.67	—	1:32

*Smoothed rates per 1000 live births using regression model on combined quinquennial data.

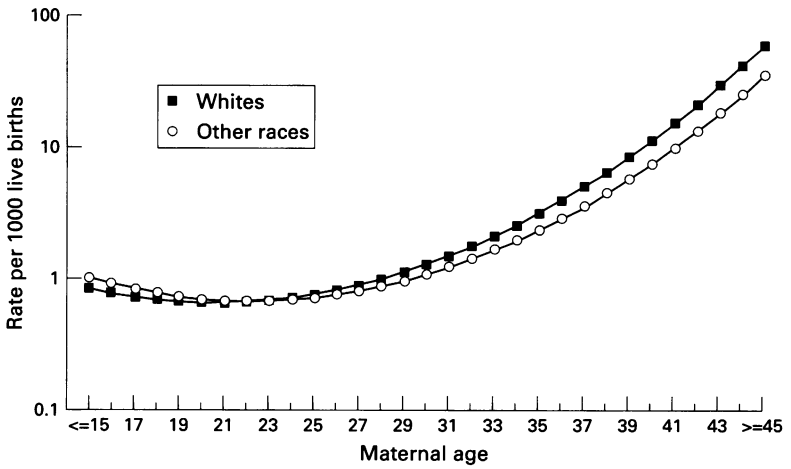

Figure 3 Comparison of smoothed single year maternal age specific risk rate estimates derived from the logistic model for combined data from south west Ohio and metropolitan Atlanta for whites and other races, 1970-1989 (per 1000 live births).

listed on Ohio birth certificates for 1970-1983 were obtained from the Division of Data Services, Ohio Department of Health.

Down syndrome cases identified from these birth certificates were determined to be true cases or false positives through the comparison of names with people karyotyped from cytogenetic laboratories within the state, or through a review of medical records at the infant's hospital of birth. This was accomplished either by members of our staff visiting the hospitals and reviewing individual records, or by medical record staffers (or physicians) at individual hospitals reviewing the records and certifying that a particular infant did in fact have Down syndrome. We determined that 5.9% of the cases with Down syndrome listed on birth certificates were false positives.[14 15] These subjects were removed from the database and the number of remaining true cases were used as the initial numerator in calculating risk rates.

To estimate the incidence of under-reporting, Huether *et al*[10] examined birth certificates of 1296 infants with Down syndrome, as determined from cytogenetic analysis, and found that 475 (36.7%) of these cases were identified on the birth certificate. This is the probability that a live birth with Down syndrome would be correctly designated on the birth certificate. Thus, the correction for under-reporting on the birth certificate was made by dividing the numerators by 0.367. Details regarding this data set for 1970-1979 and these procedures are reported by Huether *et al*.[10] We updated these estimates by including data from 1980-1983, by correcting for false positive Down syndrome cases listed on birth certificates, and by making appropriate corrections for the use of prenatal diagnosis. Data on infants born to residents of Ohio during the 14 year period were obtained from the Division of Data Services, Ohio Department of Health.

CORRECTING LIVE BIRTH DATA FOR ELECTIVELY TERMINATED PREGNANCIES INVOLVING FETUSES WITH DOWN SYNDROME

For all three data sets, we multiplied the number of electively terminated pregnancies involving fetuses with Down syndrome by 0.74, which is the estimated probability that an affected fetus will survive to birth relative to that of a fetus of normal karyotype.[16] We then added this number to the number of live births with Down syndrome and used the sum as the numerator of the maternal age specific estimates. The denominator for each data set was the total number of live births occurring in the population being considered, plus the terminated affected fetuses expected to be born. Stillbirths were excluded from both the numerators and denominators of all three data sets because the level of ascertainment of stillbirths with Down syndrome and of all stillbirths was considered low. We collected data for the numerators and denominators of all three data sets by year, by maternal age, by race, and by county of residence.

SMOOTHING SINGLE YEAR MATERNAL AGE SPECIFIC RISK RATES

Logistic regression[17] was used to model the relationship between the incidence of Down syndrome and a variety of independent predictor variables, including maternal age, race, geographical location, and the interactions of

Table 4 Number of live births with Down syndrome (corrected for elective terminations) and total live births for whites in south west Ohio and metropolitan Atlanta, and observed risk rates, by maternal age quinquennia and five quaternary time periods, 1970–1989

Mat age	1970–73 DS*	1970–73 live birth	1970–73 Rate†	1974–77 DS*	1974–77 live birth	1974–77 Rate†	1978–81 DS*	1978–81 live birth	1978–81 Rate†	1982–85 DS*	1982–85 live birth	1982–85 Rate†	1986–89 DS*	1986–89 live birth	1986–89 Rate†	Total DS*	Total live births	Total Rate†
Metropolitan Atlanta																		
≤19	13	11 622	1.12	4	8607	0.46	6	7234	0.83	3	6254	0.48	4	6650	0.60	30	40 367	0.74
20–24	14	25 522	0.55	14	17 916	0.78	11	17 776	0.62	11.7	17 991	0.65	11	18 654	0.59	61.7	97 859	0.63
25–29	19	23 512	0.81	16.7	21 277	0.79	18	21 247	0.85	18	24 136	0.75	21	28 654	0.73	92.7	118 826	0.78
30–34	13	9258	1.40	12	9486	1.27	19	13 259	1.43	29	16 769	1.73	32.2	22 102	1.46	105.2	70 874	1.48
35–39	9	2616	3.44	6.5	1963	3.30	6.5	2749	2.36	16.0	5069	3.16	34.3	7742	4.43	72.3	20 139	3.59
40–44	10	553	18.08	1.7	295	5.90	3.5	285	12.25	9.0	409	21.88	17.1	943	18.18	41.3	2485	16.63
≥45	3	33	93.75	1.7	17	108.75	1.5	8	186.25	0	9	0	0	18	0	6.2	85	75.98
Totals	81	73 116	1.11	56.7	59 561	0.95	65.5	62 558	1.05	86.7	70 637	1.23	119.7	84 763	1.41	409.4	350 635	1.17
South west Ohio																		
≤19	15	20 284	0.74	11	18 235	0.60	10	16 613	0.60	8	13 721	0.58	8	12 693	0.63	52	81 546	0.64
20–24	30	44 658	0.67	18	35 124	0.51	33	37 801	0.87	26	33 931	0.77	24	29 162	0.82	131	180 676	0.73
25–29	29	34 436	0.84	31	33 421	0.93	32	35 670	0.90	40	36 962	1.08	30.5	36 996	0.82	162.5	177 485	0.92
30–34	24	14 448	1.66	29	12 782	2.27	21	16 471	1.27	27.5	19 455	1.41	28.5	23 448	1.22	130	86 604	1.50
35–39	18	5456	3.30	19	3695	5.14	23	3659	6.28	31.9	4879	6.54	28.4	6460	4.40	120.4	24 149	4.98
40–44	18	1411	12.76	17	823	20.66	9	644	13.94	13.7	621	22.09	15.2	757	20.09	72.9	4256	17.13
≥45	2	72	27.78	2	43	46.51	2	30	66.67	0	13	0	0.7	21	35.24	6.7	179	37.65
Totals	136	120 765	1.13	127	104 123	1.22	130.0	110 888	1.17	147.1	109 582	1.34	135.4	109 537	1.24	675.5	554 895	1.22

*Down syndrome live births and fetuses (× 0.74 probability of survival). (Totals do not always add up owing to rounding.)
†Per 1000 live births.

Table 5 Number of live births with Down syndrome (corrected for elective terminations) and total live births for other races in south west Ohio and metropolitan Atlanta, and observed risk rates, by maternal age quinquennia and five quaternary time periods, 1970–1989

Mat age	DS*	1970–73 live birth	Rate†	DS*	1974–77 live birth	Rate†	DS*	1978–81 live birth	Rate†	DS*	1982–85 live birth	Rate†	DS*	1986–89 live birth	Rate†	DS*	Total live births	Rate†
Metropolitan Atlanta																		
≤19	9	10 646	0.85	3	9506	0.32	12	9592	1.25	5	8860	0.56	6	10 246	0.59	35	48 850	0.72
20–24	9	11 121	0.81	4	10 841	0.37	9	13 316	0.68	12	14 008	0.86	17	18 150	0.94	51	67 436	0.76
25–29	8	6034	1.33	4	7801	0.51	11	10 725	1.03	9	11 761	0.77	10.7	16 020	0.67	42.7	52 341	0.82
30–34	3	2719	1.10	7	3141	2.19	8	5231	1.51	8	6541	1.21	8	9667	0.82	34	27 299	1.24
35–39	2	1089	1.84	6	1004	5.98	5.7	1293	4.44	5.4	1950	2.77	12	3507	3.42	31.1	8843	3.52
40–44	4	296	13.51	2.7	218	12.57	5.2	214	24.44	1.7	236	7.37	5.5	468	11.63	19.2	1436	13.37
≥45	0	16	0	0	18	0	0	10	0	0	15	0	0	6	0	0	61	0
Totals	35	31 921	1.10	26.7	32 529	0.82	51.0	40 381	1.26	41.1	43 371	0.95	59.2	58 064	1.02	213.0	206 266	1.03
South west Ohio																		
≤19	10	7826	1.28	8	6823	1.17	6	6734	0.89	3	6138	0.49	1	7021	0.14	28	34 542	0.81
20–24	4	7983	0.50	7	7335	0.95	6	9463	0.63	10	9128	1.10	6	9393	0.64	33	43 302	0.76
25–29	1	4441	0.22	1	4747	0.21	7	6021	1.16	6	6397	0.94	5	7090	0.70	20	28 696	0.70
30–34	0	2307	0	0	1981	0	1	2620	0.38	4	3178	1.26	3	3683	0.81	8	13 769	0.58
35–39	2	1067	1.87	1	672	1.49	3	760	3.95	2.7	934	2.93	5.5	1256	4.37	14.2	4689	3.03
40–44	4	308	12.99	0	180	0	1.7	175	9.94	2	152	13.16	1.7	157	11.08	9.5	972	9.76
≥45	1	25	40.00	0	13	0	1	9	111.11	0	4	0	0	16	0	2	67	29.85
Totals	22	23 957	0.92	17	21 751	0.78	25.7	25 782	1.00	27.7	25 931	1.07	22.2	28 616	0.78	114.7	126 037	0.91

*Down syndrome live births and fetuses (× 0.74 probability of survival). (Totals do not always add up owing to rounding.)
†Per 1000 live births.

these factors. We used a stepwise approach to enter and delete variables into and out of various models and thus to compare the goodness of fit of the models until a final model was chosen. The PROC LOGISTIC[18] procedure of the Statistical Analysis System was used to implement the logistic regression analysis. This procedure allowed us to determine which variables had a statistically significant effect on single year risk rate estimates, and thus whether they should be included in the regression equation.

Table 6 Birth certificate reports for whites with Down syndrome (corrected for elective termination and false positives), total live births, reported risk rates per 1000 live births, rates corrected for birth certificate under-reporting, and smoothed rates using the logistic and CPE models, by single year maternal age, for Ohio 1970–1983

Maternal age	Down syndrome	Live births	Rate per 1000 births	Corrected rate*	Logistic derived rate†	CPE derived rate‡
≤15	4.69	14 361	0.33	0.89	0.82	0.62
16	4.00	31 556	0.13	0.35	0.77	0.62
17	11.39	58 718	0.19	0.53	0.73	0.62
18	11.69	86 648	0.14	0.37	0.70	0.63
19	27.08	113 332	0.24	0.65	0.68	0.64
20	28.40	126 094	0.23	0.61	0.68	0.65
21	41.60	137 010	0.30	0.83	0.68	0.66
22	35.60	147 035	0.24	0.66	0.69	0.67
23	33.00	154 182	0.21	0.58	0.71	0.69
24	47.22	153 738	0.31	0.84	0.74	0.72
25	45.55	148 831	0.31	0.83	0.79	0.76
26	46.79	140 365	0.33	0.91	0.85	0.81
27	47.55	128 241	0.37	1.01	0.92	0.87
28	32.76	113 829	0.29	0.79	1.02	0.95
29	39.27	97 647	0.40	1.10	1.14	1.07
30	37.56	80 573	0.47	1.27	1.30	1.22
31	31.78	64 795	0.49	1.34	1.50	1.41
32	30.33	50 936	0.60	1.62	1.75	1.67
33	25.71	40 161	0.64	1.74	2.08	2.02
34	24.29	31 496	0.77	2.10	2.49	2.48
35	27.21	24 136	1.13	3.07	3.04	3.08
36	23.12	18 611	1.24	3.38	3.75	3.88
37	24.66	13 936	1.77	4.82	4.69	4.94
38	36.33	10 737	3.38	9.22	5.95	6.34
39	24.36	8167	2.98	8.13	7.66	8.19
40	33.34	5963	5.59	15.23	9.98	10.66
41	14.09	4185	3.37	9.17	13.18	13.90
42	15.62	2834	5.51	15.02	17.62	18.22
43	12.12	1708	7.09	19.33	23.85	23.91
44	14.93	962	15.52	42.29	32.65	31.47
45	6.95	467	14.88	40.56	45.13	41.44
46	5.95	220	27.05	73.71	62.90	54.69
47	1.22	90	13.60	37.06	88.15	72.16
48	0.00	21	0.00	0.00	123.71	95.38
≥49	1.00	22	45.46	123.86	172.90	126.00

*Corrected rates were obtained by dividing the reported rates by the percentage of reporting: 0.367.
†For logistic model, equation in Results was used, with a=−4.428226, c=−0.282680, e=0.006961.
‡For CPE model, risk rate $=a+e^{(b+cx)}$, where $a=2.24370\times10^{-4}$, b=−16.82000, c=0.28053.

The variables we considered were the first order effects of the two race categories, 31 age groups, and two geographical locations; the three interaction terms of each of the pairs of variables; the square and the cube of age; and the three way interaction of race, age, and location. We used only the metropolitan Atlanta and south west Ohio data sets to calculate and smooth single year maternal age specific risk rate estimates.

Results

RISK RATE ESTIMATES FOR SOUTH WEST OHIO AND METROPOLITAN ATLANTA

Of the variables analysed for their effect on risk rate estimates, only age, age^2, race, and race by age interaction were found to have a statistically significant effect ($p<0.01$ for age, age^2, and race by age; $0.01<p<0.05$ for race). Thus, the final logistic regression equation used to calculate the single year risk rates (per 1000 live births) was:

$$\text{risk rate}=1000\{1/1+e^{-[a+b(\text{race})+c(\text{age})+d(\text{race}\times\text{age})+e(\text{age}^2)]}\}$$

where a=−4.061283, b=0.541575, c=−0.317749, d=−0.023771, e=−0.007638, and where race was defined as 0 for whites and 1 for races other than whites.

Table 1 provides the observed data on whites used for calculating the age specific estimates, and table 2 provides these data for races other than whites. These tables also provide the observed risk rate estimates for each race category for both south west Ohio and metropolitan Atlanta. Because initial comparisons between the two populations within each race showed them to be statistically similar ($\chi^2=0.0$, 1 df, $p>0.95$), the two populations were combined for each race category when comparing rates between races and calculating final risk rate estimates. However, because the rates of the two race categories were found to be significantly different ($\chi^2=4.91$, 1 df, $0.01<p<0.05$), the smoothed rates derived from logistic regression are shown separately for each race in tables 1 and 2. The data in these tables were also used to calculate regression derived rates by quinquennial (five

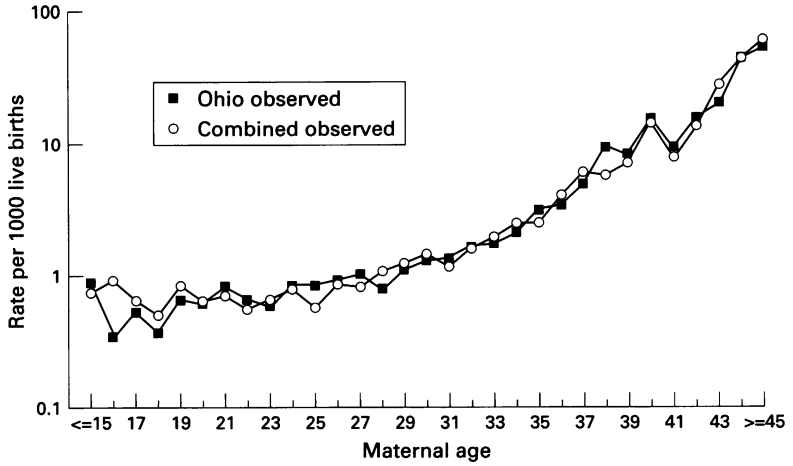

Figure 4 Comparison of observed single year maternal age specific risk rates from the state of Ohio, and combined data sets for south west Ohio and metropolitan Atlanta for whites, 1970-1983 (per 1000 live births).

year) maternal age intervals for the two race categories in table 3.

Fig 1 shows observed rates in Atlanta and in Ohio contrasted with regressed rates for whites, and fig 2 shows the corresponding rates for races other than whites. The observed rates among whites in the Ohio population are greater than those predicted in 18 of the 31 age categories, whereas the observed rates among whites in Atlanta are higher in 11 age categories. For races other than whites, observed rates were higher in 12 age categories for Ohio and in 15 for Atlanta. Fig 3 contrasts the regression derived rates for the two race categories, showing that the risk of having a child with Down syndrome in races other than whites is slightly higher for women <20 years of age, but that the risk for whites becomes progressively greater compared with races other than whites for women >25 years of age. Since the great majority of "other" races are blacks (75% in metropolitan Atlanta and 93% in south west Ohio; 86% overall), these estimates for races other than whites can be considered principally estimates for blacks. (Blacks could not be estimated alone because a number of fetuses with Down syndrome were classified only as other races.)

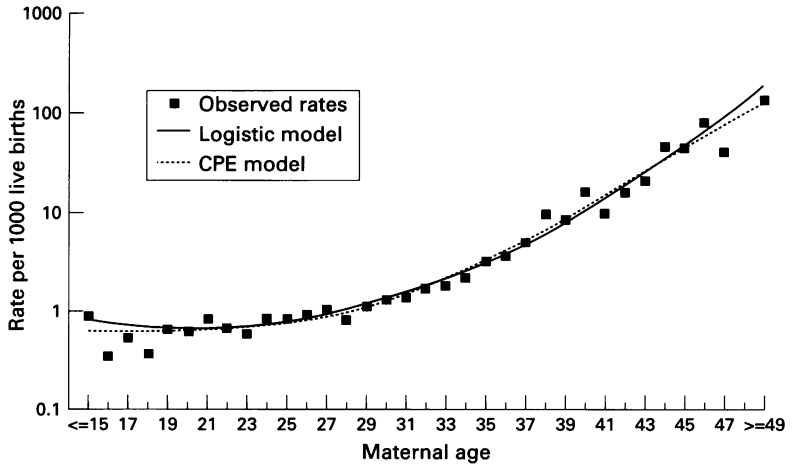

Figure 5 Comparison of smoothed single year maternal age specific risk rate estimates derived from the logistic and CPE models based upon data from the state of Ohio for whites, 1970-1983 (per 1000 live births).

TEMPORAL COMPARISONS OF RISK RATE ESTIMATES

These data were also tested to determine whether the maternal age specific risk rate estimates changed significantly during the 20 year study period. They are presented separately for the two populations by quinquennial maternal age categories for five four year time periods in table 4 for whites and in table 5 for races other than whites. Using the logistic procedure we determined that the four variables of age, age^2, race, and age × race had the same statistically significant effects in the quinquennial analysis as they did in the single year analysis, but we found no significant effect associated with temporal period nor with any of the first order interactions of temporal period with age, race, or population. The summary χ^2 for these four variables was 3.88 with 4 degrees of freedom ($0.3<p<0.5$). These results clearly indicate that quinquennial maternal age specific risk rates among the five four year periods were in good agreement and that the variation observed among cells is the result of small sample sizes.

RISK RATE ESTIMATES FOR THE STATE OF OHIO

In contrast to the Down syndrome data collected from south west Ohio and metropolitan Atlanta, which we presume represent complete ascertainment, data for the entire state of Ohio were obtained through birth certificates, long known to be grossly under-reported. Because we corrected these data for under-reporting (using cytogenetics data to estimate the level of under-reporting, as described in the Methods section), comparison of these data sets provides a useful opportunity to contrast two quite different methods of data collection for risk rate estimation. Table 6 presents (for whites only) the observed number of cases with Down syndrome (those reported on birth certificates corrected for false positives, plus cases detected prenatally and electively terminated), and observed single year maternal age specific risk rate estimates corrected for under-reporting in Ohio during 1970-1983. A statistical comparison of these corrected risk rate estimates with those from the combined observed data on whites from south west Ohio and metropolitan Atlanta (from table 1 data) is not appropriate because they derive from estimated values for both the rates by maternal age and percentages of under-reporting in the state of Ohio data set. However, as can be seen in a visual comparison of the observed (corrected) risk rate values for the two data sets for 1970-1983 in fig 4, these disparate methods of estimating maternal age risk rates show remarkable agreement.

Besides providing a basis for comparing two different means of data collection, the birth certificate data from the state of Ohio also provide a basis for comparing two methods of obtaining smoothed risk rate estimates. Goodwin[19] used these birth certificate data to calculate smoothed risk rate estimates by using a non-linear maximum likelihood regression equation, referred to as the constant plus exponential (CPE) model.[20] To compare with the CPE model, the same logistic procedure that

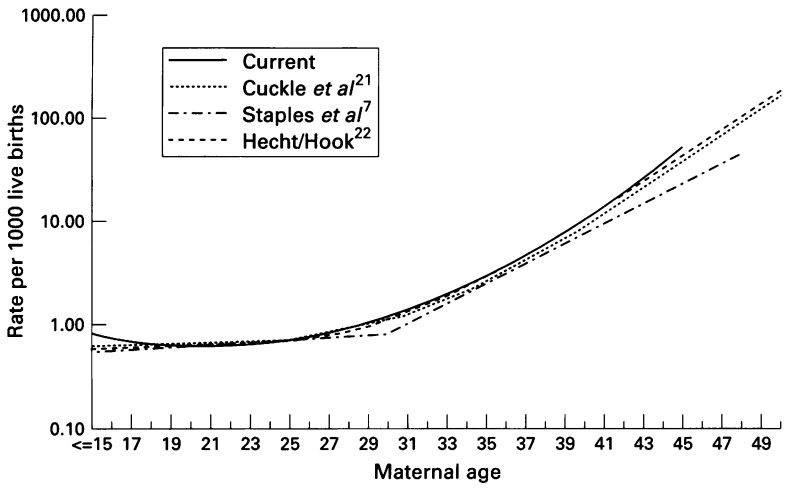

Figure 6 Comparison of smoothed single year maternal age specific risk rate estimates for whites from table 7.

Table 7 Comparison of smoothed single year maternal age specific risk rates for whites from table 2 with smoothed rates for whites from three other studies

Maternal age	Current study (table 2)	Cuckle et al[21] (table 1)	Staples et al[7] (table 6)	Hecht/ Hook[22] (table IV)
15	0.82	0.63	0.56	0.59
16	0.75	0.64	0.57	0.60
17	0.71	0.64	0.59	0.60
18	0.67	0.64	0.60	0.60
19	0.65	0.65	0.62	0.61
20	0.64	0.65	0.63	0.62
21	0.63	0.66	0.65	0.63
22	0.64	0.68	0.67	0.64
23	0.66	0.69	0.69	0.66
24	0.68	0.71	0.70	0.68
25	0.72	0.74	0.72	0.71
26	0.78	0.78	0.74	0.75
27	0.85	0.83	0.76	0.81
28	0.94	0.89	0.78	0.88
29	1.06	0.98	0.80	0.98
30	1.21	1.10	0.82	1.12
31	1.40	1.26	1.02	1.30
32	1.65	1.46	1.28	1.54
33	1.97	1.74	1.59	1.86
34	2.39	2.11	1.99	2.29
35	2.94	2.60	2.48	2.87
36	3.68	3.26	3.09	3.64
37	4.68	4.13	3.86	4.67
38	6.03	5.29	4.81	6.06
39	7.88	6.85	6.01	7.91
40	10.46	8.93	7.49	10.39
41	14.08	11.76	9.35	13.70
42	19.22	15.38	11.67	18.14
43	26.58	20.41	14.56	24.08
44	37.18	27.03	18.17	32.04
45	52.55	35.71	22.67	42.69
46		47.62	28.29	56.94
47		66.67	35.30	76.01
48		90.91	44.05	101.54
49		125.00		135.72
50		166.67		181.46

we used to smooth the risk rate estimates in tables 1 and 2 was also used on these data. These estimates and those from the CPE model are presented in table 6 and contrasted graphically in fig 5. Although, again, no statistical test is applicable for comparing these smoothed risk rates, fig 5 shows that they produce very similar results. The estimates differ by more than 10% only for maternal ages <=17 and >=46 years; for mothers of these ages, the CPE model appears to fit the observed data somewhat better than the logistic model.

Discussion

We found that the quinquennial maternal age specific risk rate estimates for Down syndrome over the five four year time periods remained stable throughout the 20 years (tables 4 and 5). These findings are consistent with those of most other published studies in which such temporal comparisons of risk rates have been possible. We also found that the observed single year maternal age specific risk rates for whites derived from two disparate methods of obtaining data produced very similar results (fig 4), a finding that is consistent with those of other studies.[21] The database from all of Ohio also allowed a direct comparison of the capacity of the CPE and logistic models to smooth the maternal age specific risk rates. Table 6 and fig 5 show the close agreement of the rates obtained by using these models, as only seven of the 31 pairs of single year maternal age specific rates differ by more than 10%, while only three differ by more than 20%. Given the ease of use and wide availability of the logistic procedure, these similar results indicate it will probably be the method of choice for smoothing future estimates of single year maternal age specific rates, even though the CPE model appears to fit these observed data somewhat more closely at the two extremes.

ESTIMATES OF MATERNAL AGE SPECIFIC RISK RATES FOR WHITES

Our major objective in this study was to estimate single year and quinquennial maternal age specific risk rates for both whites and other races using two populations believed to have highly ascertained cases of Down syndrome among both live births and fetuses of electively terminated pregnancies. The estimates for whites only may be compared with those from the other 10 studies providing single year maternal age specific rate estimates.[1-10] Cuckle *et al*[21] compared data from eight of the nine studies available at that time (excluding only the early data of Collmann and Stoller[1]), and concluded that "while the results of individual surveys differed, the general pattern (in all eight studies) was very similar", and so produced a combined risk using a weighted average of the separate risk estimates. They then smoothed these rates using the CPE model, producing the risk rates apparently used most frequently today in genetic counselling settings. Hecht and Hook[22] made slight modifications in the combined data set used by Cuckle *et al*,[21] but produced almost identical risk rate estimates. However, Hecht and Hook[22] also argued the best estimates may be obtained by using data from only two of the eight studies most likely to have been completely ascertained.[6 23] They combined these data into the "likely complete data subset," and, again using the CPE model, produced separate estimates.

These estimates obtained by Cuckle *et al*[21] and Hecht and Hook[22] are useful for comparison with those we found. Additionally, because Staples *et al*[7] published their estimates after Cuckle *et al*, and have the only other data set besides ours that includes data after 1980, we compare in table 7 the smoothed rates for whites from table 1 with those from these three other data sets, and compare them graphically

in fig 6. Although there is essentially complete agreement among the four sets of rates for women in their 20s, we found somewhat higher rates for those under 20, and increasingly higher rates for those over 30 years of age. The risk rate estimates from Hecht and Hook[22] are closest to ours, which is consistent with these data coming from the two studies they believe most completely ascertained. Of the 31 single year maternal age comparisons, they differ by more than 10% in only six age categories (15-18 and 44-45), and by more than 20% in just three (15-16 and 45). In these cases, our data provide higher risk rates estimates. The estimates that are uniformly the lowest of the four studies come from Australia[7]; interestingly, they are also among the lowest of any of the published studies, even though these authors believe their data also represent virtually complete ascertainment. The average risk rates from the combined data of Cuckle *et al*[21] are the second lowest of the four studies. Our estimated rates are more than 10% higher than those of Cuckle *et al* in 18 of the 31 single year maternal age categories, and more than 20% in five of them (15, 42 to >=45). This comparison suggests that the data at present being used for genetic counselling purposes for whites may be underestimating the risks for Down syndrome at the early and late maternal ages.

COMPARISON OF MATERNAL AGE SPECIFIC RISK RATES FOR OTHER RACES

Since 86% of "other" races are blacks in both the metropolitan Atlanta and south west Ohio live birth data sets, the single year maternal age estimates for races other than whites can be considered principally as estimates for blacks. They were statistically different from whites. Whether these differences are real (that is, biologically significant) is unclear. There is some question as to whether cases were ascertained as thoroughly for other races in south west Ohio as they were for whites in that population or as they were for other races in metropolitan Atlanta. The abstraction of cases in south west Ohio was probably more reliant on initial physician diagnosis, and discussions with both obstetricians and paediatricians suggest they sometimes have a more difficult time diagnosing Down syndrome in blacks than in whites. It is also possible that blacks may not go to paediatricians as often as whites for follow up diagnosis. Additionally, Krivchenia *et al*[24] calculated expected rates of Down syndrome among live births for both whites and other races in metropolitan Atlanta and south west Ohio for this time period and found the observed frequency to be 92% of that expected for each race category in Atlanta, whereas it was 103% for whites but only 83% for other races in south west Ohio. Finally, when the combined Down syndrome rates from the combined populations for whites (from table 1) were compared with rates for other races in Atlanta alone (table 2), there was good agreement ($\chi^2=1.39$, $0.1<p<0.3$), but the combined rates for whites were significantly higher than rates for other races in south west Ohio alone ($\chi^2=3.88$, $0.01<p<0.05$).

Few studies have been conducted to determine maternal age specific risk rates for Down syndrome in races other than whites. Early studies of comparative rates among whites and blacks generally considered only birth prevalence, and did not take into account maternal age structure differences. Sever *et al*,[25] who may have been the first to estimate quinquennial maternal age specific risk rates among blacks and to compare them with rates among whites, found them similar. However, their results were based upon 63 total cases. Stark and White[26] also compared five year maternal age specific rates between whites and blacks and also found them similar except for significantly lower rates in blacks for women >=40. This was probably because of underascertainment according to Hook and Porter,[27] who concluded "there is no definitive evidence that there are any consistent differences between races in the incidence of Down's syndrome births". This conclusion was recently refined by Hook[28] who stated there is no consistent evidence "for differences in maternal age-specific rates" between whites and blacks. A similar conclusion was reached by Bell.[29]

However, in a report incorporating data from 17 state surveillance programmes in the United States involving a total of 7.8 million live births, CDC researchers found that quinquennial maternal age specific Down syndrome rates for blacks <35 years old were significantly lower than those for whites, but that quinquennial rates for those >=35 years of age were similar between the two races.[30] Interestingly, because this study does not account for the effect of prenatal diagnosis and selective pregnancy termination on the number of children born with Down syndrome, the basis for the latter finding could be that blacks >=35 years of age use amniocentesis much less frequently than do whites, as shown by Brett *et al*.[31] Kuppermann *et al*[32] also found this to be true, which they suggest is why blacks and other races in California have a significantly higher risk than whites for women >=35 years of age. Differential use of prenatal chromosome diagnosis among races could be the basis for both of these disparate results, depending upon the level of use between blacks and whites in each population, thus complicating any comparisons of risk rates among older women without having good prenatal diagnosis data. Additionally, underascertainment of infants with Down syndrome born to blacks could also be a factor in the finding by CDC that women <=35 years old have significantly lower risks, given that in 10 of the 17 states supplying data for their study data were not collected by trained abstractors.

This issue of potential underascertainment of Down syndrome among blacks will need to be resolved before a definite statement regarding maternal age specific risk rate similarities or differences between these two races can be made. In the meantime, to our knowledge, our study is the first to provide single year maternal age specific risk rates for other races who are

predominantly blacks; we hope that these rates will prove useful for genetic counselling purposes. We believe that the rates found for whites, based upon the most recent data available, also provide valuable estimates for genetic counselling. Future studies such as this may become increasingly difficult if not impossible to carry out in the United States, given the problems of collecting prenatal analysis data from laboratories that are geographically so widespread and have such limited patient data available.

The following cytogenetic laboratories/genetics programmes and their Directors are gratefully acknowledged for providing data on fetuses karyotyped with Down syndrome: Dr Jean H Priest, Cytogenetic Laboratory, Emory University, Atlanta; Dr Shirley Soukup, Children's Hospital Cytogenetic Laboratory, Cincinnati; Dr Harold Chen, Children's Hospital Cytogenetics Laboratory, Dayton; Dr Walter Johnson (deceased), Case Western Reserve University Cytogenetic Laboratory, Cleveland; Dr Richard Juberg (deceased), Cytogenetics, Ultra-Chem Laboratories, Dayton; Dr Maureen McCorquodale, Medical College of Ohio Cytogenetic Laboratory, Toledo; Dr Irwin Schafer, Cleveland Metro Health Medical Center Genetics Program; Dr Richard Stallard, Children's Hospital Cytogenetic Laboratory, Columbus, OH; Dr Tom Tegenkamp, Cytogenetics Laboratory, St Elizabeth Hospital, Dayton; Dr John Waterson, Akron Genetics Center, Children's Hospital, Akron; Ms Judy Betts, Genetics Associate, Youngstown Hospital Association, Youngstown; Mr Willard Yarma, Cytogenetics Laboratory, Kettering Medical Center, Dayton; Mr Joseph Yoder, Cytogenetics Laboratory, Aultman Hospital, Canton, OH; Dr Rina Schmidt, Director, Cytogenetics Laboratory, Metpath Inc, Teterboro, NJ; Dr Richard Warren, Director, Genetic Associates of Miami; Ms Linda Downs, Director, Genetic Services Inc, Atlanta; Dr Navnit Mitter, Dr Berry, Directors, Cytogenetic Laboratory, Genetics and Laboratory Medicine Inc, Atlanta; Dr Stirling Puck, Director, Cytogenetics Laboratory, Vivigen Inc, Santa Fe, NM. We also gratefully acknowledge data analysis assistance of Ms Jane Khoury, Department of Environmental Health, University of Cincinnati.

1 Collmann RD, Stoller A. A survey of mongoloid births in Victoria, Australia, 1942-1957. *Am J Public Health* 1962;**52**:813-29.
2 Trimble BK, Baird PA. Maternal age and Down syndrome: age-specific incidence rates by single-year intervals. *Am J Med Genet* 1978;**2**:1-5.
3 Hook EB, Lindsjo A. Down syndrome in live births by single-year maternal age interval in a Swedish study: comparison with results from a New York State study. *Am J Hum Genet* 1978;**30**:19-27.
4 Sutherland GR, Clisby SR, Bloor G, Carter RF. Down's syndrome in South Australia. *Med J Aust* 1979;**2**:58-61.
5 Young ID, Williams EM, Newcombe RG. Down syndrome and maternal age in South Glamorgan. *J Med Genet* 1980; **17**:433-6.
6 Koulischer L, Gillerot Y. Down's syndrome in Wallonia (South Belgium), 1971-1978: cytogenetics and incidence. *Hum Genet* 1980;**54**:243-50.
7 Staples AJ, Sutherland GR, Haan EA, Clisby S. Epidemiology of Down syndrome in South Australia, 1960-1989. *Am J Hum Genet* 1991;**49**:1014-24.
8 Hook EB, Chambers GM. Estimated rates of Down syndrome in live births by one year maternal age intervals for mother aged 20-49 in a New York State study—implications of the risk figs for genetic counseling and cost-benefit analysis of prenatal diagnosis programs. *Birth Defects* 1977;**XIII**(3A):123-41.
9 Hook EB, Fabia JJ. Frequency of Down syndrome in live births by single-year maternal age interval: results of a Massachusetts study. *Teratology* 1978;**17**:223-8.
10 Huether CA, Gummere GR, Hook EB, *et al.* Down's syndrome: percentage reporting on birth certificates and single-year maternal age risk-rates for Ohio 1970-79: comparison with upstate New York data. *Am J Public Health* 1981;**71**:1367-72.
11 Zarfas DE, Wolf LC. Maternal age patterns and the incidence of Down's syndrome. *Am J Ment Defic* 1979;**83**: 353-9.
12 Barsel-Bowers G, Abuelo DN, Pueschel SM. Incidence of Down's syndrome in Rhode Island. *JAMA* 1982;**248**:645.
13 Edmonds LD, Layde PM, James LM, Flynt JW, Erickson JD, Oakley GP. Congenital malformations surveillance: two American systems. *Int J Epidemiol* 1981;**10**:247-52.
14 Goodwin BAS, Huether CA. Revised estimates and projections of Down syndrome births in the United States, and the effects of prenatal diagnosis utilization, 1970-2002. *Prenat Diagn* 1987;7:261-71.
15 Johnson KM, Huether CA, Hook EB, *et al.* False-positive reporting of Down syndrome on Ohio and New York birth certificates. *Genet Epidemiol* 1985;**2**:123-31.
16 Hook EB, Topol BB, Cross PK. The natural history of cytogenetically abnormal fetuses detected at midtrimester amniocentesis which are not terminated electively: new data and estimates of the excess and relative risk of late fetal death associated with 47,+21 and some other abnormal karyotypes. *Am J Hum Genet* 1989;**45**:855-61.
17 Hosmer DW, Lemeshow S. *Applied logistic regression.* New York: John Wiley, 1989.
18 18SAS Institute Inc. *SAS/STAT Uuer's guide, version 6.* 4th ed. Vol 2. Cary, NC: SAS Institute Inc,1989:846.
19 Goodwin BAS. *Estimation and projection of Down's syndrome births for the United States, and the effects of amniocentesis utilization, 1970-2002.* Masters thesis, University of Cincinnati, Ohio, 1985.
20 Lamson SH, Hook EB. A simple function for maternal-age-specific rates for Down syndrome in the 20-to-49 year range and its biological implications. *Am J Hum Genet* 1980;**32**:743-53.
21 Cuckle HS, Wald NJ, Thompson SG. Estimating a woman's risk of having a pregnancy associated with Down's syndrome using her age and serum alpha-fetoprotein level. *Br J Obstet Gynaecol* 1987;**94**:387-402.
22 Hecht CA, Hook EB. The imprecision in rates of Down syndrome by 1-year maternal age intervals: a critical analysis of rates used in biochemical screening. *Prenat Diagn* 1994;**14**:729-38.
23 Lindsjo A. Down's syndrome in Sweden: an epidemiological study of three-year material. *Acta Paediatr Scand* 1974;**63**: 571-6.
24 Krivchenia EL, Huether CA, Edmonds LD, May D, Guckenberger SA. A comparative epidemiology of Down syndrome in two United States populations, 1970-1989. *Am J Epidemiol* 1993;**137**:815-28.
25 Sever JL, Gilkeson MR, Chen TC, Ley AC, Edmonds D. Epidemiology of mongolism in the collaborative project. *Ann NY Acad Sci* 1970;**171**:328-40.
26 Stark CR, White NB. Cluster analysis and racial differences in risk of Down's syndrome. In: Hook EB, Porter IH, eds. *Population cytogenetics.* New York: Academic Press, 1977; 275-83.
27 Hook EB, Porter IH. Human population cytogenetics: comments on racial differences in frequency of chromosome abnormalities, putative clustering of Down's syndrome, and radiation studies. In: Hook EB, Porter IH, eds. *Population cytogenetics.* New York: Academic Press, 1977:353-65.
28 Hook EB. Chromosome abnormalities: prevalence, risks and recurrence. In: Brock D *et al*, eds. *Prenatal diagnosis and screening.* Edinburgh: Churchhill Livingstone, 1992:351-92.
29 Bell JA. The epidemiology of Down's syndrome. *Med J Aust* 1991;**155**:115-17.
30 CDC. Down syndrome prevalence at birth-United States, 1983-1990. *MMWR CDC Surveill Summ* 1994;**43**:617-22.
31 Brett KM, Schoendorf KC, Kiely JL. Differences between black and white women in the use of prenatal care technologies. *Am J Obstet Gynecol* 1994;**170**:41-6.
32 Kuppermann M, Gates E, Washington AE. Racial-ethnic differences in prenatal diagnostic test use and outcomes: preferences, socioeconomics, or patient knowledge? *Obstet Gynecol* 1996;**87**:675-82.